SYNTHESIS OF SOME 1,3-DIAZINES

BY

DAVID YARROW CURTIN

A.B., Swarthmore College, 1943

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN CHEMISTRY
IN THE GRADUATE SCHOOL OF THE
UNIVERSITY OF ILLINOIS, 1945

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SYNTHESIS OF SOME 1,3-DIAZINES*

PART I

2-AMINO-4-METHYL-6-METHOXYMETHYLPYRIMIDINE AND RELATED COMPOUNDS

Although a very large volume of research has recently been directed toward finding a good antimalarial, the complexity of the disease is such that the problem is still unsolved. Those drugs which have been found to be practical therapeutic agents almost without exception have been derivatives of quinoline or acridine, such as are quinine and atabrine.

Certain sulfa drugs, however, have shown activity against malaria and for this reason it was thought desirable to prepare some other compounds of this type for testing.

The purpose of the present research was to modify sulfamethazine (2-sulfanilamido-4,6-dimethylpyrimidine) by the introduction of functional groups into the molecule which, it was hoped, would decrease its toxicity and increase its activity. Accordingly the synthesis of 2-sulfanilamido-4-methyl-6-X-methylpyrimidine and 2-sulfanilamido-5-bromo-6-X-methylpyrimidine was attempted where X is hydroxy, methoxy or amino.

2-Amino-4-methyl-6-methoxymethylpyrimidine (I) was prepared by the condensation of methoxyacetylacetone with guanidine carbonate, a reaction completely analogous to that of acetylacetone reported by Combes and Combes.[1] Compound I reacted smoothly with N^4-acetylsulfanilyl chloride or *p*-nitrobenzenesulfonyl chloride in pyridine[2] to give 2-(N^4-acetylsulfanilamido)-4-methyl-6-methoxymethylpyrimidine (II) or

*This work was carried out under a contract recommended by the Committee on Medical Research between the office of Scientific Research and Development and the University of Illinois.

2-(*p*-nitrobenzenesulfonamido)-4-methyl-6-methoxymethylpyrimidine (III) which could be hydrolyzed or reduced respectively to 2-sulfanilamido-4-methyl-6-methoxymethylpyrimidine (IV). III was brominated with bromine in aqueous potassium bromide solution to give 2-(N^4acetylsulfanilamido)-5-bromo-4-methyl-6-methoxymethylpyrimidine which was hydrolyzed to 2-sulfanilamido-5-bromo-4-methyl-6-methoxymethylpyrimidine (V). IV and V have been tested for antimalarial activity and found to be much less active than sulfadiazine or quinine*

Attempts to cleave the ether linkage of I, II and III with a number of reagents were unsuccessful. I with cold 48% hydrobromic acid or hydrobromic acid in glacial acetic acid gave a compound believed to be 2,7-diamino-4,9-dimethylpyrimido[4,5-g]quinazoline (VI). This belief is supported by the ultraviolet absorption spectra of I and of the cleavage product. VI was tested for antimalarial activity and found to be inactive.*

2-Hydroxy-4-methyl-6-methoxymethylpyrimidine hydrochloride (VII) was prepared by the treatment of methoxyacetylacetone with urea, a method analogous to that used by Evans[3] for the preparation of 2-hydroxy-4,6-dimethylpyrimidine (VIII). VII, on treatment with phosphorous oxychloride was converted to 2-chloro-4-methyl-6-methoxymethylpyrimidine (IX). This reaction is analogous to that previously reported for VIII.[4]

2-Amino-5-bromo-4-methyl-6-methoxymethylpyrimidine (X) was prepared by bromination of I with an aqueous solution of bromine and potassium bromide. Attempts to cleave the ether linkages in VII, IX and X were unsuccessful.

*Tests were carried out by E. K. Marshall, Johns Hopkins School of Medicine; E. M. K. Geiling, University of Chicago; L. H. Schmidt, Cincinnati College of Medicine, and A. P. Richardson, University of Tennessee.

The chlorination of one of the methyl groups of 2-amino-4,6-dimethylpyrimidine (XI) or its benzenesulfonyl derivative with sulfuryl chloride failed, as did the attempted acetoxylation of VIII with lead tetraacetate. An attempt to prepare 2-chloro-4-(β-hydroxyethyl)-6-methylpyrimidine by converting IX to its lithium salt and treating the latter with formaldehyde was also unsuccessful.

PART II

4-(4-Diethylamino-1-Methylbutylaminoq-7-Chloroquinazoline

The great promise shown by 4-(4-diethylamino-1-methylbutylamino)-7-chloroquinazoline as an antimalarial suggested the desirability of preparing and testing its quinazoline analogue, 4-(4-diethylamino-1-methylbutylamino)-7-chloroquinazoline (XII).

The method used was similar to that used by Magidson and Golovchinskaya[5] for the preparation of some other alkylaminoalkylaminoquinazolines. 4-Chloroanthranilic acid (XIII) was obtained from R. A. Bauman and D. M. Burness, who prepared it by treating 2,4-dichlorobenzoic acid with aqueous ammonia and copper powder in an autoclave, a method described in a German Patent.[6] XIII was heated with formamide to give 4-hydroxy-7-chloroquinazoline (XIV). XIV was converted to 4,7-dichloroquinazoline with phosphorous pentachloride and the latter compound was treated with 4-amino-1-diethylaminopentane to give XII.

XII was tested for antimalarial activity and found to have a quinine equivalent of 1 against duck malaria and 2 against chick malaria.*

*Tested by E. K. Marshall, Jr., Johns Hopkins School of Medicine, and E. M. K. Geiling, University of Chicago.

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VITA

The author was born in Philadelphia, Pennsylvania, on August 22, 1920. He attended the elementary school of Webster Springs, West Virginia, and Webster Springs High School and graduated from George School, Bucks County, Pennsylvania, in June, 1939. He entered Swarthmore College in the fall and received the degree of Bachelor of Arts in February, 1943. The same month he entered the Graduate School of the University of Illinois as a teaching assistant. He held this position for one semester and since then has worked as a special research assistant on the anti-malarial program of the Office of Scientific Research and Development.

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